Preliminary Comments on the ISA from Dr. Joel G. Pounds

Comments on Chapter 4 – Exposure, Toxicokinetics, and Biomarkers

The third draft of this chapter is very well organized and well written. I am particularly pleased with the lucid description of topic strengths, weaknesses, and limitations introductory found in many of the introductory and concluding sections. The authors of Chapter 4 have done a very nice job of explaining and applying mechanistic and empirical models to illustrate scenarios of changing exposure levels, duration of Pb exposure, and other Pb exposure scenarios and the interpretation of blood and bone Pb levels as biomarkers of exposure.

Page 58. The review and analysis of the potential contribution of ALAD alleles is fair but this paragraph needs to draw a conclusion as ALAD polymorphisms are the most widely recognized genetic determinants of blood Pb. This conclusion may be little more than the contribution of ALAD alleles is inconclusive and the underlying causes of discrepancies among studies remains to be elucidated.

Page 4-41 – The ISA authors might consider speculating (I'm not aware of any data) on the potential role of the human microbiome in modulating Pb bioassessibility. There is considerable environmental microbiology literature

Page 4-60. Figure 4-7 Legend is a little confusing. Is Child B "elevated" Pb intake of 5.5 ug per day on top of the baseline 10 ug/d? Should be 55ug/d? Is there a reason this simulation used a 10 ug/d baseline when several other simulations in this chapter used 3.2 ug/d?

Page 4-70 Figures 4-9. Is "bone" total skeletal lead? See comment on Figure 4-7. Blood Pb peaks at ~ 8 ug/dL with an intake of ~38 ug/d, while Child B (Figure 4-7) peaks at ~20 ug/dL with a smaller Pb intake?

Page 4-83 Figure 4-15 legend. This legend might note the Leggett model inputs for this simulation. That the "switch" for RBC saturation is turned on, and the RBC concentration for saturation. Question, How was RBC saturation handled in Figure 12- (high exposure in adults)?

Page 4-88. Figure 4-17. Can you clarify the meaning of "at baseline" means for this figure.

Table 4-9. This table could be modified to note how the papers cited handled censored data. The text includes a nice description of the issues related to application of XRF measurements to population studies. But, how the authors dealt with missing or negative data affects the conclusions that can be drawn from this table using the tabulated mean and SD.

Add model papers from David Flemming and Anna Steenhout for completeness?

Trivial editorial comments

Consider renaming, Exposure, Toxicokinetics, and Biomarkers to Exposure, Toxicokinetics, and Biomarkers of Exposure.

P4-63 Teeth. I recall a couple papers describing the heterogeneity of Pb in longitudinal sections of teeth using PIXE or SRIXE. Joel will look for those papers.

P4-65 Line 26. Contribute 40- → contribute as much as 40% (because relative contribution depends on all sources of Pb to blood.

P4-68 Line 28 by resorption → by bone resorption

P4-68 Line 29 – This sentence is a little confusing. Bone Pb half-times depend on bone turnover rates, bone resorption, age, The apparent bone half-times may during increased Pb exposure and contribution to bone.

Page 4-45,

Line 14 this… → limited binding capacity
Line 16. This… → This process…

Page 4-55 Line 22 This… → This uncertainty…

Page 4-69 line 4. This… → This concept…

Page 4-84 Line 84. This… → This observation…

Page 4-84 Title Studies of Pb Biomarker Levels → Studies of Biomarkers of Pb Exposure

Page 4-139 Line 18 They… → These models…

Page 4-139 Line 21 They… → These models

Page 4-139 Line 23 confidence in… → confidence in individual…

Page 4-142 Line 12 diffuses to… → diffuse to kinetically…

Page 4-142 Title for 4.7.3 Pb Biomarkers → Biomarkers of Pb Exposure